

Non-*HFE* Hepatic Iron Overload

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ABSTRACT

Numerous clinical entities have now been identified to cause pathologic iron accumulation in the liver. Some are well described and have a verified hereditary basis; in others the genetic basis is still speculative, while in several cases nongenetic iron-loading factors are apparent. The non-*HFE* hemochromatosis syndromes identifies a subgroup of hereditary iron loading disorders that share with classic *HFE*-hemochromatosis, the autosomal recessive trait, the pathogenic basis (i.e., lack of hepcidin synthesis or activity), and key clinical features. Yet, they are caused by pathogenic mutations in other genes, such as transferrin receptor 2 (*TFR2*), hepcidin (*HAMP*), hemojuvelin (*HJV*), and ferroportin (*FPN*), and, unlike *HFE*-hemochromatosis, are not restricted to Caucasians. Ferroportin disease, the most common non-*HFE* hereditary iron-loading disorder, is caused by a loss of iron export function of FPN resulting in early and preferential iron accumulation in Kupffer cells and macrophages with high ferritin levels and low-to-normal transferrin saturation. This autosomal dominant disorder has milder expressivity than hemochromatosis. Other much rarer genetic disorders are associated with hepatic iron load, but the clinical picture is usually dominated by symptoms and signs due to failure of other organs (e.g., anemia in atransferrinemia or neurologic defects in aceruloplasminemia). Finally, in the context of various necro-inflammatory or disease processes (i.e., chronic viral or metabolic liver diseases), regional or local iron accumulation may occur that aggravates the clinical course of the underlying disease or limits efficacy of therapy.

KEYWORDS: Iron overload, non-*HFE* hemochromatosis, transferrin receptor 2, hepcidin, ferroportin, hemojuvelin

The liver is the main source of the iron-regulatory hormone hepcidin and plays a central role in the homeostatic control of iron traffic in the body. Although intestinal iron absorption is tightly regulated to sustain hemoglobin synthesis and critical cell functions, there is no active mechanism for iron excretion from the body.¹ This exposes humans to a substantial risk for iron overload and iron-driven toxicity, particularly in the liver, the principal iron storage site in the body. Excess iron, in solution with oxygen, may generate free radical formation

via Fenton and Haber-Weiss chemistry, with hydrogen peroxide (H_2O_2), being changed into its noxious hydroxyl radical ($HO\cdot$). This leads to consequent damage to DNA, proteins, and membranes.² The classic example of iron overload in human pathology is *HFE*-hereditary hemochromatosis (HC), but numerous other entities are now identified to cause pathologic iron accumulation in the liver³ (Table 1). Some are well described and have a verified hereditary basis, whereas in others the genetic and hereditary basis is still speculative. A large percentage

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Table 1 Common Causes of Non-*HFE* Iron Overload or Mis-Distribution in Humans

Iron Overload		Iron Mis-Distribution	
Hereditary		Hereditary	
Disorder/Cause	Pattern of Iron Accumulation	Disorder/Cause	Pattern of Iron Accumulation
Non- <i>HFE</i> hereditary hemochromatosis (TFR2-, HJV-, HAMP-, FPN-related)	Systemic	X-linked sideroblastic anemias	Systemic (mitochondria)
Ferroportin disease (classic form)	Systemic	Friedreich ataxia	Systemic (mitochondria)
Aceruloplasminemia	Systemic		
Atransferrinemia	Systemic		
DMT-1 deficiency	Regional (mainly liver)		
H-ferritin related iron overload	Systemic		
Hereditary iron-loading anemias with inefficient erythropoiesis	Systemic (early hepatic iron load due to increased iron absorption)		
Acquired		Acquired	
Disorder/Cause	Pattern of Iron Accumulation	Disorder/Cause	Pattern of Iron Accumulation
Oral	Systemic	Anemia of chronic diseases	Systemic (macrophages)
Parenteral	Systemic		
Posttransfusion	Systemic (preferential iron accumulation in macrophages)		
Chronic liver diseases (viral- and alcohol-related; NASH)	Regional (liver)		
Neurodegenerative disorders	Regional (brain)		
Miscellaneous			
Disorder/Cause	Pattern of Iron Accumulation		
Porphyria cutanea tarda	Systemic (mainly liver)		
African siderosis	Systemic		
Alloimmune (neonatal) hemochromatosis	Systemic		

TFR2, transferrin receptor-2; *HAMP*, hepcidin; *HJV*, hemojuvelin; *FPN*, ferroportin; NASH, nonalcoholic steatohepatitis.

reflect systemic iron overload, others, in the context of a necro-inflammatory, or in as yet unknown disease processes, results in regional or local iron accumulation (e.g., chronic liver diseases) (Table 1). Finally, an increasingly recognized class of iron disorders is due to disrupted intracellular (e.g., Friedreich ataxia) or body iron traffic (e.g., anemia of chronic diseases) leading to iron misdistribution despite a normal total body iron content (Table 1). Here we will discuss causes and consequences of most common hereditary or acquired disorders associated with hepatic iron overload beyond *HFE*-hemochromatosis.

HEREDITARY DISORDERS

Non-*HFE* Hereditary Hemochromatosis

Hemochromatosis, or hereditary hemochromatosis, has been historically considered a unique clinicopathologic entity likely due to a single gene defect. This view seemed to be confirmed in 1996 when a single-gene

polymorphism was found in most hemochromatotic patients worldwide⁴(see also Olynyk et al elsewhere in this issue). However, as genetic testing for *HFE* became more widespread and nearly one-fifth of HC patients turned out to lack the pathogenic p.Cys282Tyr change, it rapidly became clear that the situation was more complicated than previously thought.⁵ Other iron genes whose mutations were associated with hereditary iron overload syndromes with some, or many, or apparently even all of the phenotypic features of classic HC, were reported: transferrin receptor 2 (*TFR2*),⁶ hepcidin (*HAMP*),⁷ hemojuvelin (*HJV*),⁸ and ferroportin (*FPN*) (Table 1).^{9,10}

Today, the term non-*HFE* hereditary hemochromatosis embraces all forms of HC nonlinked to the common *HFE* p.Cys282Tyr polymorphism, and thus far associated with pathogenic mutations of *TFR2*, *HJV*, *HAMP*, and in rare cases, the *FPN* gene. These non-*HFE* hemochromatosis syndromes share with classic *HFE*-HC key features, namely (1) early and progressive expansion of the plasma iron compartment (increasing

transferrin saturation [TS]), which precedes tissue iron overload (increasing serum ferritin [SF]); (2) progressive and preferential iron deposits in parenchymal cells with potential for severe damage and disease that may involve liver, endocrine glands, heart, and joints; (3) nonimpaired erythropoiesis and optimal response to therapeutic phlebotomy; and (4) inadequate hepcidin synthesis or activity.³ These similarities with *HFE*-HC stem from the fact that—beyond their genetic diversities—all known hemochromatoses belong to the same clinicopathologic entity, as they all originate from the failure to prevent unneeded iron from entering the circulatory pool due to hepcidin deficiency (see also, Babitt and Lin, this issue; and below). Depending on the gene involved and its role in hepcidin regulation, the phenotype of HC varies, ranging from the severe *HJV*- and *HAMP*-juvenile forms, to the relatively milder adult-onset *TFR2* and *FPN* phenotypes.

EPIDEMIOLOGY

Unlike *HFE*, none of the non-*HFE*-HC genes appears to be restricted to northern European descent. Most cases of *TFR2*-HC represent largely inbred families of Italian extraction with high consanguinity.^{11–15} However, pathogenic mutations of *TFR2* have also been identified in other ethnicities, including Asian populations.^{16–21} In Asians, where *HFE*-HC is almost nonexistent, *TFR2*-HC seems a common form of hereditary HC. Reported *TFR2* mutations include missense and nonsense, deletions, and frameshifts, followed by a premature stop codon and alternative splicing mutations (Table 2).

Although most *FPN* mutations give rise to a distinct form of hereditary iron overload called ferroportin disease⁷² (see below), unusual *FPN* mutations are believed to cause rare forms of HC similar to *HFE*-HC.^{28–31,33,35,36,38}

Most cases of so-called juvenile HC (JHC) are due to mutations of *HJV*, formerly *HFE2*.⁸ Many *HJV* pathogenic mutations have been reported;^{42,54,55,57} one, p.Gly320Val, seems more common than others as it has been found in most reported pedigrees worldwide (Table 2).^{8,34,42,43,46,47,51,58–61}

The study of additional cases with JHC identified a cohort demonstrating mutations in *HAMP*, the gene encoding hepcidin, on chromosome 19q13.⁷ *HAMP*-HC is much rarer than *HJV*-HC, and only few cases have been reported so far.^{34,64–66,69–71} The concept and spectrum of JHC has been further extended by the identification of patients with combined mutations for *HFE* and *TFR2* presenting with a severe hemochromatotic syndrome identical to JHC.²⁴

In addition, there is evidence that selected *HJV* and *HAMP* mutations, when carried simultaneously with mutant *HFE*, may aggravate and accelerate the course of classic HC (Table 2).^{45,48,53,67,68}

PATHOGENESIS

The first biochemical manifestation of all forms of HC, regardless of the pathogenic gene involved, is an increase of TS that reflects an uncontrolled influx of iron into the bloodstream from enterocytes and macrophages.⁷³ As the body has no effective means of significantly reducing plasma iron levels, without therapeutic intervention, overload in the plasma compartment will lead to the progressive accumulation of iron in the parenchymal cells of key organs, creating a distinct risk for oxidative damage. The time of onset and pattern of organ involvement in HC vary depending on the rate and magnitude of plasma iron overloading, which depends in turn on the underlying genetic mutation. The latter determines the extent of hepcidin deficiency and eventually the rate and magnitude of body iron loading. For this reason, milder adult-onset forms (e.g., *TFR2*- and *FPN*-related) and more severe juvenile-onset forms (e.g., *HJV*- and *HAMP*-related) of HC are recognized. Iron release from enterocytes and macrophages into the bloodstream in humans is under the control of the hepcidin–ferroportin axis. It now seems that most non-*HFE* HC genes play a role in conveying the iron signal to hepcidin, although the details of this process are not fully uncovered (see Babitt and Lin, this issue). In the rare cases of *FPN*-HC, instead *FPN* mutations are thought to impair hepcidin-triggered *FPN* degradation and/or *FPN* internalization/degradation (see De Domenico, Ward, and Kaplan, this issue).⁷⁴

CLINICAL ASPECTS

In view of the genetic and pathogenic considerations expressed above, HC can be seen as a genetically heterogeneous disease that results from the complex interaction between genetic and acquired factors. If the altered gene plays a dominant role in hepcidin synthesis/activity (e.g., *HAMP* itself or *HJV*), circulatory iron overload occurs rapidly and reaches high levels. In these cases, the modifying effects of acquired environmental and lifestyle factors will be negligible and the clinical presentation will invariably be dramatic, with early onset (first to second decade) of a full-blown organ disease.³ In contrast, p.Cys282Tyr *HFE* homozygosity results in a genetic predisposition that requires the concurrence of host-related or environmental factors to produce disease (see also, Gan, Powell, and Olynyk, this issue). As mentioned, co-inherited mutations in other HC genes, such as *HAMP* and *HJV*, may have a role in disease penetrance of *HFE*-HC, but they are rare.^{45,48,53,67,68}

The clinical appearance of *TFR2*-HC patients mimics that of *HFE*-hereditary HC, namely patients with high TS and SF and low penetrance in premenopausal women.¹³ Age range is somewhat younger, but

Table 2 Non-HFE Hemochromatosis: Reported Gene Mutations

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
TFR2 (RefSeq NM_003227.3, NP_003218.2)					
1	c.64G>A	p.Val22Ile	Missense (heterozygous)	Postulated effect on iron status	22
2	c.88_89insC	p.Arg30ProfsX31	Frameshift (homozygous)	Hemochromatosis	12
3	c.313C>T	p.Arg105X	Nonsense (homozygous)	Hemochromatosis	18
4	c.515T>A	p.Met172Lys	Missense (homozygous)	Hemochromatosis	12,14
5	c.614+4A>G		Splicing (homozygous)	Hemochromatosis	23
6	c.750C>G	p.Tyr250X	Nonsense (homozygous)	Hemochromatosis	6,11
7	c.949C>T	p.Gln317X	Nonsense (homozygous)	Hemochromatosis	24
8	c.1186C>T	p.Arg396X	Nonsense (compound heterozygous with p.Gly792Arg or c.1538-2A>G)	Hemochromatosis	15,20
9	c.1231_1233del3	p.Asn411del	Deletion (compound heterozygous with p.Ala444Thr)	Hemochromatosis	25
10	c.1330G>A	p.Ala444Thr	Missense (compound heterozygous with p.Asn411del)	Hemochromatosis	25
11	c.1364G>A	p.Arg455Gln	Missense (heterozygous)	Putative modifier in p.Cys282Tyr HFE homozygous	26
12	c.1403G>A	p.Arg468His	Missense (homozygous)	Hemochromatosis	21
13	c.1469T>G	p.Leu490Arg	Missense (homozygous)	Hemochromatosis	19
14	c.1538-2A>G		Splicing (compound heterozygous with p.Arg396X)	Hemochromatosis	15
15	c.1665delC	p.Ser556AlafsX6	Frameshift (homozygous)	Hemochromatosis	19
16	c.1861_1872del12	p.Ala621_Gln624del	Deletion (homozygous)	Hemochromatosis	13,17
17	c.2069A>C	p.Gln690Pro	Missense (homozygous)	Hemochromatosis	16
18	c.2137-1G>A		Splicing (homozygous)	Hemochromatosis	25
19	c.2374G>A	p.Gly792Arg	Missense (compound heterozygous with p.Arg396X)	Hemochromatosis	20
SLC40A1 (RefSeq NM_014585.5, NP_055400.1)					
1	c.-59_-45del15		Deletion (heterozygous)	Hemochromatosis*	27
2	c.190T>A	p.Tyr64Asn	Missense (heterozygous)	Hemochromatosis	28
3	c.430A>C	p.Asn144His	Missense (heterozygous)	Hemochromatosis	29
4	c.430A>G	p.Asn144Asp	Missense (heterozygous)	Hemochromatosis	30
5	c.431A>C	p.Asn144Thr	Missense (heterozygous)	Hemochromatosis	31
6	c.718A>G	p.Lys240Glu	Missense (heterozygous)	Hemochromatosis*	32
7	c.977G>A	p.Cys326Tyr	Missense (heterozygous)	Hemochromatosis*	33,34
8	c.977G>C	p.Cys326Ser	Missense (heterozygous)	Hemochromatosis	35
9	c.1014T>G	p.Ser338Arg	Missense (heterozygous)	Hemochromatosis	36
10	c.1502A>G	p.Tyr501Cys	Missense (heterozygous)	Hemochromatosis*	37
11	c.1520A>G	p.His507Arg	Missense (heterozygous)	Hemochromatosis	38
HJV (RefSeq NM_213653.3, NP_998818.1)					
1	c.81delG	p.Leu28SerfsX24	Frameshift (homozygous)	Juvenile hemochromatosis	39
2	c.160A>T	p.Arg54X	Nonsense (homozygous)	Juvenile hemochromatosis	40
3	c.196G>T	p.Gly66X	Nonsense (homozygous)	Juvenile hemochromatosis	41

Table 2 (Continued)

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
4	c.220delG	p.Val74TrpfsX40	Frameshift (compound heterozygous with p.Asn269LysfsX43)	Juvenile hemochromatosis	42
5	c.238T>C	p.Cys80Arg	Missense (compound heterozygous with p.Leu101Pro or p.Arg326X)	Juvenile hemochromatosis	43,44
6	c.239G>A	p.Cys80Tyr	Missense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	34
7	c.253T>C	p.Ser85Pro	Missense (homozygous)	Juvenile hemochromatosis	42
8	c.295G>A	p.Gly99Arg	Missense (homozygous or compound heterozygous with p.Leu101Pro)	Juvenile hemochromatosis	34,42
9	c.296G>T	p.Gly99Val	Missense	Juvenile hemochromatosis	8
10	c.302T>C	p.Leu101Pro	Missense (homozygous or compound heterozygous with p.Cys80Arg or p.Gly99Arg; heterozygous)	Juvenile hemochromatosis Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous when heterozygous	42,43,45
11	c.314C>T	p.Ser105Leu	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	45
12	c.346C>T	p.Gln116X	Nonsense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	46
13	c.356G>T	p.Cys119Phe	Missense (homozygous)	Juvenile hemochromatosis	47
14	c.391_403del13	p.Arg131PhefsX115	Frameshift (homozygous)	Juvenile hemochromatosis	42
15	c.404T>G	p.Leu135Arg	Missense (heterozygous)	Putative modifier in p.His63Asp <i>HFE</i> homozygous	48
16	c.445delG	p.Asp149ThrfsX97	Frameshift (homozygous)	Juvenile hemochromatosis	42
17	c.494T>A	p.Leu165X	Nonsense (homozygous)	Juvenile hemochromatosis	49
18	c.503C>A	p.Ala168Asp	Missense (homozygous)	Juvenile hemochromatosis	42
19	c.509T>C	p.Phe170Ser	Missense (homozygous)	Juvenile hemochromatosis	42
20	c.512G>T	p.Gly171Val	Missense (homozygous)	Juvenile hemochromatosis	50
21	c.516C>G	p.Asp172Glu	Missense (compound heterozygous with p.Cys321ValfsX21)	Juvenile hemochromatosis	42
22	c.526C>T	p.Arg176Cys	Missense (homozygous or compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	51,52
23	c.573G>T	p.Trp191Cys	Missense (homozygous)	Juvenile hemochromatosis	42
24	c.575C>T	p.Pro192Leu	Missense (homozygous)	Juvenile hemochromatosis	34
25	c.581T>C	p.Leu194Pro	Missense (homozygous)	Juvenile hemochromatosis	34
26	c.588T>G	p.Asn196Lys	Missense (heterozygous)	Putative modifier in p.Cys282Tyr/p.His63Asp <i>HFE</i> compound heterozygous	53
27	c.615C>G	p.Ser205Arg	Missense (compound heterozygous with p.Gly250Val)	Juvenile hemochromatosis	42

Table 2 (Continued)

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
28	c.665T>A	p.Ile222Asn	Missense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	8,43
29	c.745G>C	p.Asp249His	Missense (homozygous)	Hemochromatosis in middle age	54
30	c.749G>T	p.Gly250Val	Missense (compound heterozygous with p.Ser205Arg)	Juvenile hemochromatosis	42
31	c.806_807insA	p.Asn269LysfsX43	Frameshift (compound heterozygous with p.Val74TrpfsX40)	Juvenile hemochromatosis	42
32	c.842T>C	p.Ile281Thr	Missense (homozygous or compound heterozygous with p.Cys321X)	Juvenile hemochromatosis	8,55
33	c.862C>T	p.Arg288Trp	Missense (homozygous)	Juvenile hemochromatosis	42,56
34	c.904G>A	p.Glu302Lys	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	45
35	c.934C>T	p.Gln312X	Nonsense (homozygous)	Juvenile hemochromatosis	54,57
36	c.959G>T	p.Gly320Val	Missense (homozygous or compound heterozygous; heterozygous)	Juvenile hemochromatosis	8,34,42–44,46,47,51,58–61
				Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous when heterozygous	45
37	c.960_961insG	p.Cys321ValfsX21	Frameshift (homozygous)	Juvenile hemochromatosis	42
38	c.963C>G	p.Cys321Trp	Missense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	43
39	c.963C>A	p.Cys321X	Nonsense (compound heterozygous with p.Ile281Thr)	Juvenile hemochromatosis	55
40	c.976C>T	p.Arg326X	Nonsense (compound heterozygous with p.Cys80Arg or p.Gly320Val)	Juvenile hemochromatosis	8,44
41	c.982_985del4	p.Ser328AspfsX10	Frameshift (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	47
42	c.985C>T	p.Arg329X	Nonsense (homozygous)	Juvenile hemochromatosis	62
43	c.1004G>A	p.Arg335Gln	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	45
44	c.1026delT	p.Ala343ProfsX24	Frameshift (homozygous)	Juvenile hemochromatosis	34
45	c.1080delC	p.Cys361ValfsX6	Frameshift (homozygous)	Juvenile hemochromatosis	8
46	c.1114A>G	p.Asn372Asp	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	45
47	c.1153C>T	p.Arg385X	Nonsense (homozygous)	Juvenile hemochromatosis	42
HAMP (RefSeq NM_021175.2, NP_066998.1)					
1	c.-153C>T		Promoter mutation (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	63
2	c.-25G>A		Promoter mutation (homozygous)	Juvenile hemochromatosis	64–66
3	c.95delG	p.Gly32Aspfs	Frameshift (homozygous)	Juvenile hemochromatosis	7
4	c.126_127del2	p.Arg42Serfs	Frameshift (homozygous)	Juvenile hemochromatosis	34

Table 2 (Continued)

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
5	c.148_150 + 1del4	p.Met50del	Frameshift (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> heterozygous	67
6	c.166C>T	p.Arg56X	Nonsense (homozygous; heterozygous)	Juvenile hemochromatosis Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous when heterozygous	7,68
7	c.175C>G	p.Arg59Gly	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous and heterozygous	68
8	c.208T>C	p.Cys70Arg	Missense (homozygous)	Juvenile hemochromatosis or hemochromatosis	69,70
9	c.212G>A	p.Gly71Asp	Missense (heterozygous)	Putative modifier in p.Cys282Tyr <i>HFE</i> homozygous	67,68
10	c.233G>A	p.Cys78Tyr	Missense (homozygous)	Juvenile hemochromatosis	71
Gene <i>TFR2</i> + <i>HFE</i>					
1	<i>HFE</i> : c.187C>G/ c.845G>A <i>TFR2</i> : c.949C>T	<i>HFE</i> : p.His63Asp/ p.Cys282Tyr <i>TFR2</i> : p.Gln317X	<i>HFE</i> missense and <i>TFR2</i> nonsense (digenic inheritance: <i>HFE</i> compound heterozygous and <i>TFR2</i> homozygous)	Juvenile hemochromatosis	24

TFR2, transferrin receptor-2; *SLC40A1*, ferroportin; *HJV*, hemojuvelin; *HAMP*, hepcidin.

*Reports of patients with a classic hemochromatosis phenotype but lacking confirmatory liver histopathology.

with slower progression of iron overload than in JHC. Although relatively few cases have been documented, the liver pathology is again described as strongly resembling *HFE*-hereditary HC with early iron deposition in periportal hepatocytes (see Deugnier and Turlin, this issue). Most demonstrate a milder degree of iron overload than those with *HFE*-HC, although there is progression to cirrhosis in some published cases. The variability in clinical expressivity may also depend on the underlying *TFR2* defect that may have different effects on hepcidin expression and the resulting iron-loading phenotype. The diagnosis is made by clinical presentation, serum iron indices, and exclusion of the *HFE* genotype. The leading diagnostic clue is usually, as in the case of the other non-*HFE* HC syndromes, unexplained hyperferritinemia (Fig. 1). Treatment, as in the case of classic hereditary HC, is by venesection.

Most reported cases of *FPN*-HC refer to patients with clinical manifestations identical to *HFE*- (or *TFR2*-) HC with high TF and SF levels, predominant hepatic parenchymal iron overload, and cirrhosis and organ failure in advanced cases.^{29–31,35} As in the other forms of HC, phlebotomy appears to be well tolerated and effective.

HJV-HC accounts for almost all cases of JHC, the most severe form of human HC, known for decades as a distinct clinicopathologic entity. The first reports date back to the 1950s.⁷⁵ Lamon⁷⁶ first reviewed all published cases and described the main clinical features of JHC. The syndrome differs considerably from *HFE*-HC with respect to age, an almost equal ratio between sexes, greater frequency of cardiac and endocrine disturbances.^{77–80} The patient usually presents in the second decade, typically with hypogonadism that manifests as primary infertility in the female. A dilated cardiomyopathy that often becomes refractory to treatment is a common complication; the untreated patient usually dies of cardiac disease by the 30th year. The hepatic complications of iron overload in JHC may seem not as common as in the case of adult forms of HC (*HFE*-, *TFR2*-, and *FPN*-HC), but this may be simply because the clinical picture is dominated by the endocrine and cardiac failure. In fact, the hepatic pathology may be profound, with histologically diagnosed cirrhosis developing even at a young age in up to 40% of patients. However, the clinical diagnosis of JHC is often coincidental, relating to investigation of endocrine or cardiac abnormalities including cardiac

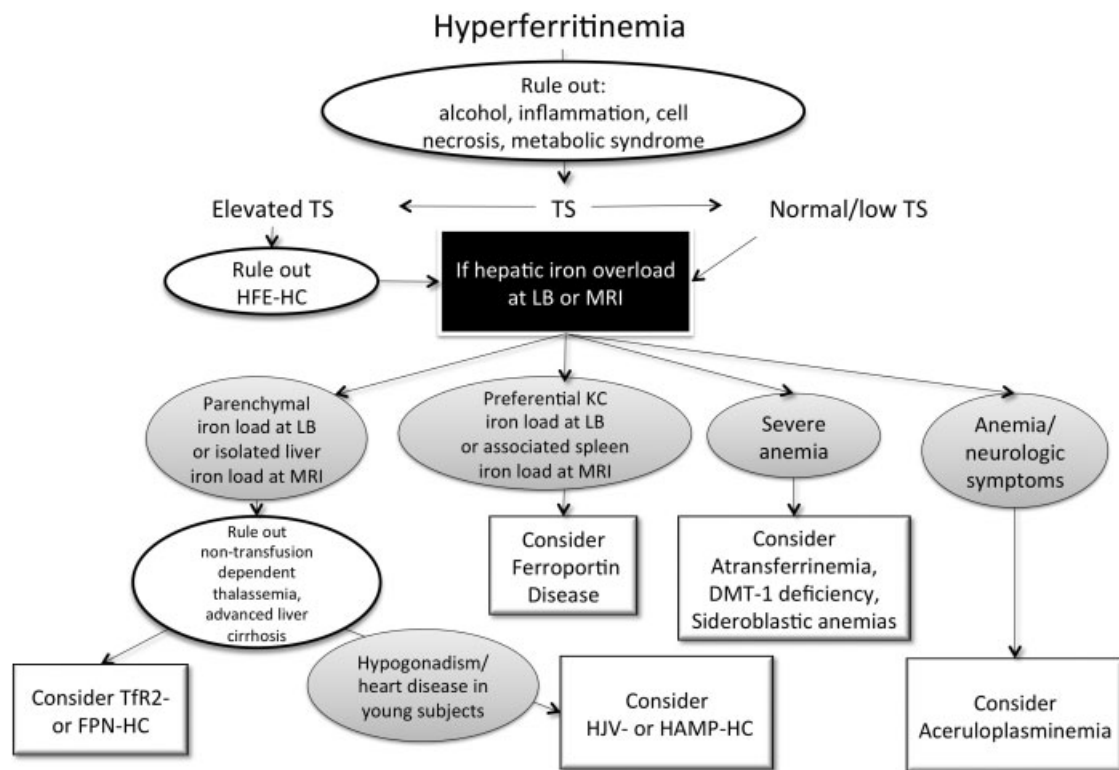


Figure 1 In patients with unexplained hyperferritinemia, regardless of the level of serum iron, cofactors and comorbidities associated with increased serum ferritin (SF) (e.g., chronic alcohol consumption, metabolic disturbances, obesity, inflammation, etc.) should be considered first. In the absence of these comorbidities, or if the iron abnormalities persist after these conditions have been effectively treated. If transferrin saturation (TS) is persistently elevated, *HFE*-hemochromatosis (HC) should be excluded by genetic testing. If *HFE* test is not diagnostic, parenchymal iron overload must be confirmed, ideally by liver biopsy (LB), before considering non-*HFE*-HC. Parenchymal iron overload in adults, in the absence of thalassemia intermedia/nontransfused hereditary anemias with inefficient erythropoiesis or advanced cirrhosis, is typical of *TFR2*-hemochromatosis, or more rarely, ferroportin-*(FPN)* related forms. In young patients with severe cardiomyopathy and hypogonadism, juvenile HC should be considered and hemochromatosis-*(HJV)* and hepcidin-*(HAMP)* gene sequencing performed. If available. In patients with increased SF levels and normal-low TS, in the absence of common causes of hyperferritinemia (see above), the workup should focus on documenting an iron-overload state by LB or magnetic resonance imaging (MRI). If so, depending on the pattern of iron distribution (e.g., preferential Kupffer cells, iron overload) and/or accompanying symptoms (e.g., severe anemia and/or neurologic disorders) *ferroportin disease* or other much rarer hereditary iron loading diseases can be considered (see text for details). TS, transferrin saturation.

shock. Glucose intolerance is manifest in almost two-thirds of patients and there may be presentation due to arthropathy or skin changes. Iron liver pathology in JHC are similar to those of hereditary HC in that there is progressive iron loading of parenchymal cells with typical sparing of the reticuloendothelial system (see Deugnier and Turlin, this issue). As in other forms of HC, aggressive venesection remains the cornerstone of therapy. Depending on the extent of progression of the disease, there may be a place for chelating therapy and cardiac transplant.⁷⁸

Ferroportin Disease

In 1999, when only one HC gene (i.e., *HFE*) was known, a non-*HFE* hereditary iron-overload condition

with typical reticuloendothelial iron deposits was described in a large family from Italy.¹⁰ In the wake of the discovery of ferroportin, genome-wide screening procedures confirmed that the disease gene was *SLC40A1*, coding for ferroportin, on chromosome 2q32.⁹ All patients were heterozygous for a c.230C—a substitution resulting in the replacement of alanine 77 with aspartate. This was subsequently referred to as ferroportin disease (FD).⁷²

EPIDEMIOLOGY

As opposed to *HFE*- and non-*HFE*-HC, the pattern of inheritance of FD is autosomal dominant. Therefore, either parent carries the pathogenic mutation of *FPN* and presents with unexplained hyperferritinemia. Numerous mutations of the *FPN*

gene have been identified so far in families with primary hyperferritinemia, with divergent findings with respect to the pattern of ferritin/transferrin dissociation in probands of French-Canadian, Melanesian, Thai, Asian, and European heritage (Table 3).^{9,28,34,37,38,81-98} Yet, a few common *FPN* mutations have been independently reported in different countries (e.g., p.Val162del; p.Ala77Asp; p.Gly80Ser) (Table 3).

Overall, these figures make ferroportin disease the most common form of hereditary iron overload beyond *HFE-HC*.

PATHOGENESIS

The pathogenesis is quite different from hereditary HC and is discussed in this issue by De Domenico, Ward, and Kaplan. As originally hypothesized,⁹ the disorder is due to a loss of iron-export function of *FPN*: the

Table 3 Ferroportin Disease: Reported Mutations

<i>SLC40A1</i> (RefSeq NM_014585.5, NP_055400.1)					
	Nucleotide Change	Amino Acid Change	Type of Variation*	Phenotype	Reference
1	c.134C>A	p.Ala45Glu	Missense	Ferroportin disease [†]	98
2	c.206C>T	p.Ala69Val	Missense	Ferroportin disease [†]	98
3	c.212C>T	p.Ser71Phe	Missense	Ferroportin disease [†]	98
4	c.214G>T	p.Val72Phe	Missense	Ferroportin disease	94
5	c.230C>A	p.Ala77Asp	Missense	Ferroportin disease	9,89,99
6	c.238G>A	p.Gly80Ser	Missense	Ferroportin disease	92,96,98,100,101
7	c.239G>T	p.Gly80Val	Missense	Ferroportin disease	88
8	c.262A>G	p.Arg88Gly	Missense	Ferroportin disease	27,98
9	c.263G>C	p.Arg88Thr	Missense	Ferroportin disease	91
10	c.454A>T	p.Ile152Phe	Missense	Ferroportin disease	93
11	c.469G>A	p.Asp157Asn	Missense	Ferroportin disease	94
12	c.470A>C	p.Asp157Ala	Missense	Ferroportin disease	97
13	c.470A>G	p.Asp157Gly	Missense	Ferroportin disease	85,98
14	c.473G>T	p.Trp158Leu	Missense	Ferroportin disease	98
15	c.474G>T	p.Trp158Cys	Missense	Ferroportin disease	38
16	c.484_486del3	p.Val162del	Deletion	Ferroportin disease	81-84,87,98,99,102,103
17	c.521A>T	p.Asn174Ile	Missense	Ferroportin disease	100
18	c.532C>G	p.Arg178Gly	Missense	Ferroportin disease	102
19	c.533G>A	p.Arg178Gln	Missense	Ferroportin disease	27,98
20	c.539T>C	p.Ile180Thr	Missense	Ferroportin disease	91
21	c.542A>T	p.Asp181Val	Missense	Ferroportin disease	88,98
22	c.546G>T	p.Gln182His	Missense	Ferroportin disease	85,98
23	c.553A>G	p.Asn185Asp	Missense	Ferroportin disease	98,104
24	c.554A>C	p.Asn185Thr	Missense	Ferroportin disease [†]	98
25	c.610G>A	p.Gly204Ser	Missense	Ferroportin disease [†]	98
26	c.695C>A	p.Ala232Asp	Missense	Ferroportin disease	105
27	c.698T>C	p.Leu233Pro	Missense	Ferroportin disease	93,98
28	c.744G>T	p.Gln248His	Missense	Ferroportin disease [†]	106,107
29	c.800G>A	p.Gly267Asp	Missense	Ferroportin disease	88
30	c.809A>T	p.Asp270Val	Missense	Ferroportin disease	108
31	c.968G>T	p.Gly323Val	Missense	Ferroportin disease	85
32	c.1111C>T	p.Arg371Trp	Missense	Ferroportin disease [†]	98
33	c.1112G>A	p.Arg371Gln	Missense	Ferroportin disease [†]	98
34	c.1402G>A	p.Gly468Ser	Missense	Ferroportin disease [†]	109
35	c.1466G>A	p.Arg489Lys	Missense	Ferroportin disease	110
36	c.1467A>C	p.Arg489Ser	Missense	Ferroportin disease	90
37	c.1468G>A	p.Gly490Ser	Missense	Ferroportin disease	27,98
38	c.1469G>A	p.Gly490Asp	Missense	Ferroportin disease	86

*All reported ferroportin mutations are at the heterozygous state, according to the autosomal dominant trait.

[†]Reported data do not allow to conclusively assign a classic ferroportin diseases phenotype.

resultant reduction in iron efflux causes a bottleneck in macrophages, which generate the largest iron flows, resulting in iron accumulation in Kupffer cells (KC) and macrophages with high SF levels and low to normal TS until late in the disease when TS also rises. The low-normal TS despite high SF is the biochemical hallmark of the disease, and along with the early and preferential accumulation of iron in hepatic KC (see Deugnier and Turlin, this issue) is central in the diagnostic workup of the disorder (Fig. 1). Although KC iron load is an early feature of FD and essential in the differential diagnosis with *HFE*-HC, discrete hepatocytic iron deposits are also appreciable in the classic FD, due to defective FPN activity in hepatocytes, even at early stages.¹⁰

CLINICAL ASPECTS

Clinical presentation appears heterogeneous, but overall, expressivity is milder than classic HC and the associated liver disease is usually not as severe. Hypochromic anemia is common in young females, and may require iron supplementation, which may further exacerbate the iron overload. Although venesection is again the cornerstone of therapy, it may not be tolerated equally in all patients and low TS with anemia may be rapidly established despite SF still being elevated.⁷² If phlebotomy is discontinued, there is a rapid rise in the ferritin level and both oral chelation and erythropoietin may be of some benefit. The disease must be suspected in any individual with unexplained hyperferritinemia, and investigated with serum iron studies and genetic testing, if available, of the immediate family (Fig. 1). Abdominal magnetic resonance imaging (MRI) is a useful noninvasive diagnostic tool to categorize and diagnose the disorder, as it can differentiate patients with classic FD, characterized by liver, spleen, and bone marrow iron retention, from the rarer nonclassic form of FPN-related iron load (i.e., *FPN*-HC), associated with liver iron overload, but normal spleen and bone marrow iron content.¹¹¹

Aceruloplasminemia

This is an extremely rare autosomal recessive disease, first reported by Miyajima,¹¹² described mainly in Japanese patients and due to loss of function mutations in ceruloplasmin (CP) and resulting in iron overload in the liver and pancreas and progressive neurodegeneration.^{113–115} Ceruloplasmin is a copper-containing ferroxidase synthesized by hepatocytes that catalyzes the oxidation of ferrous to ferric iron, necessary for the release of iron to plasma transferrin.^{116,117} This activity may involve the stabilization of membrane FPN.¹¹⁸ Patients develop diabetes mellitus, retinal degeneration, ataxia, and dementia

late in life.¹¹⁹ A mild-to-moderate degree of anemia with low serum iron and elevated SF is a constant feature and the pattern of hepatic iron overload is reminiscent of hereditary HC, but fibrosis or cirrhosis is uncommon. The disease should be suspected in cases presenting with anemia, high SF, and neurologic involvement. Brain MRI with typical iron accumulation in basal ganglia and thalamus may help confirm the diagnosis. Iron chelators have been used with beneficial effects.^{120,121}

Atransferrinemia/Hypotransferrinemia

An extremely rare autosomal recessive hereditary disorder, atransferrinemia, was first described in a young girl with severe hypochromic anemia, and marked generalized iron overload¹²² it, has since been described in very few families worldwide.^{122,124–128} Transferrin delivers iron to the erythroid precursors and the defect leads to decreased hemoglobin synthesis resulting in a severe microcytic hypochromic anemia. However, this in turn leads to increased intestinal absorption that, although inefficiently handled in the plasma, is efficiently imported by parenchymal cells leading to often severe parenchymal iron overload at sites including the liver, myocardium, pancreas, and thyroid. Clinical presentation and features include pallor and fatigue with high SF, serum iron, and decreased total iron-binding capacity (TIBC). Treatment may be relatively effective, at least in some patients, via combined infusion of fresh frozen plasma, and subsequent phlebotomy or chelation therapy.

DMT-1 Deficiency

Divalent metal transporter 1 (DMT1) is the protein at the apical membrane of the duodenal enterocyte that transports iron (and other divalent ions) upon reduction to its ferrous state by the brush border ferrireductase DcytB.¹²⁹ DMT1 also allows the iron exit from the acidified endosomes. Autosomal recessive mutations of DMT1 have been recently reported.^{130–135} All patients with DMT1 deficiency present with severe hypochromic microcytic anemia at birth, increased TS with normal TIBC, and slightly elevated SF, increased soluble transferrin receptor. All reported cases except one,¹³⁵ unlike the DMT1 mutant animal models, present with marked hepatic iron overload. Patients appear to respond to erythropoietin.^{136,137}

H-Ferritin-Related Iron Overload

Hyperferritinemia and concomitant hepatic iron overload have been described in four of seven members of a Japanese family carrying a heterozygous single point mutation (A49U) of the IRE motif in the

5'-untranslated region (5'UTR) of H-ferritin mRNA (+49A>T)¹³⁸. No further cases have been reported since the original series. However, an elegant animal study has recently showed that mice with an intestinal ferritin H gene deletion develop hemochromatosis,¹³⁹ indicating that intestinal ferritin H is also required to limit iron efflux from intestinal cells, and that ferritin is an iron-loading gene, at least in mice.

Hereditary Iron-Loading Anemias with Inefficient Erythropoiesis or Altered Intracellular Iron Traffic

Within the spectrum of hereditary anemias, variable iron overload in the liver may be identified not only due to transfusional iron, but also to primary abnormalities of iron metabolism (see also, Deugnier and Turlin, this issue). The thalassemias, due to inherited defects of either the α - or β - globin chains of hemoglobin, represent the most common single gene inherited disorder in the world.¹⁴⁰ Although transfusions may largely account for the iron-overload states found in these patients (see below), the characteristic ineffective erythropoietic drive likely induces excess iron absorption via inhibition of hepcidin synthesis (see Babitt and Lin, this issue) and leads to hepatic iron overload. This is especially evident in patients with thalassemia intermedia who present marked parenchymal iron overload that mimics *HFE*-HC (see also, Deugnier and Turlin, this issue). Similar mechanistic phenomena may occur in the sideroblastic hereditary (and acquired) anemias characterized by anemia with ringed sideroblasts in the bone marrow and iron overload.¹⁴¹

Liver disease, due to iron-driven oxidative damage but also to concomitant viral hepatitis, is common in β -thalassemia, the more severe and clinically important hemoglobinopathy. Standard pegylated interferon/ribavirin therapy can be successfully used in these patients¹⁴²: the aggravation of the underlying anemic state due to the hemolytic activity of ribavirin can be managed by using erythropoiesis-stimulating agents and blood transfusions. Thalassaemic patients with chronic liver disease need close hepatic ultrasound surveillance for hepatocellular carcinoma (HCC).

In X-linked sideroblastic anemia, due to mutations of delta-aminolevulinic acid synthetase 2, the primary pathogenic event is excessive deposition of mitochondrial iron (Table 1). Seemingly, in Friedreich ataxia,¹⁴³ an autosomal recessive, degenerative disease that involves the central and peripheral nervous systems and the heart, a defect in iron-sulfur cluster assembly interferes with iron export from mitochondria. These conditions represent the paradigm of a new class of iron-loading disorders due to iron mis-distribution within the

cell (Table 1), and seem to benefit from the use of iron chelators.¹⁴⁴

ACQUIRED DISORDERS

Enteral/Parenteral Iron Overload

Iron overload may arise from excessive iron introduction through the enteral or parenteral route (Table 1). Usually, it is the long-term blood transfusion for hereditary anemias or various causes of bone marrow failure (e.g., aplastic anemia, myelodysplastic syndrome, etc.), which may cause a clinically apparent iron-loading disorder. This may also be the case in transfusion-dependent anemic patients with chronic kidney disease and long-term dialysis. The iron excess, in all these cases, is derived from senescent red blood cells and will thus preferentially accumulate in KC and macrophages; it is usually associated with some architectural disturbance in the liver, whereas endocrine glands and the heart are the preferential targets of toxicity and failure. Iron chelators are the mainstay of treatment in posttransfusion iron overload.¹⁴⁵ The reporting of responses to chelation therapies has typically focused on average changes in serum ferritin in patient populations. This approach has limitations. Changes in serum ferritin may not reflect trends in iron balance equally in all patients or for all chelation regimens and provide no useful information about the proportion of responder patients. For example, this gives insufficient information about iron trends in tissues such as the heart. Recently, monitoring of iron overload and response to therapy has advanced with the increasing use of MRI techniques to estimate iron balance (changes in liver iron concentration) and extra-hepatic iron distribution (myocardial T2*).¹⁴⁶ A patient's lack of a response may result from inadequate dosing, high transfusion requirement, poor treatment adherence, or unfavorable pharmacology of the chelation regime. In fact, despite therapeutic improvements with the use of new and potent iron chelators, it is still cardiac iron overload that causes most deaths in posttransfusion iron-loading anemias.¹⁴⁵ The efficacy of iron chelation in patients with chronic kidney disease is often complicated by the presence of a chronic inflammatory state that leads to iron sequestration in the reticuloendothelial system and prevents iron redistribution.¹⁴⁷

Chronic Liver Diseases

Common chronic liver diseases, including viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, and HCC, are often associated with varying degrees of iron loading.¹⁴⁸ This may be of low grade, but is sometimes sufficiently severe as to mistakenly identify hereditary HC, although this is less of a problem after the introduction of genotyping. Important questions still

have to be answered, however. These include the relationship between iron and the primary disease as well as its possible association with the various types of hereditary HC. Recent advances in the understanding of the iron regulatory genes and in particular hepcidin increasingly support a direct relationship between disease progression and a pathogenic role for iron. Pathologic and diagnostic aspects and the role of liver biopsy in hepatic iron overload found in the course of various liver diseases is discussed by Deugnier and Turlin (this issue).

MISCELLANEOUS DISORDERS

Several human diseases due to both hereditary (clearly identified or suspected) and acquired disorders are characterized by iron accumulation in the liver.

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT), the most common porphyria, is caused by a deficiency of uroporphyrinogen decarboxylase activity (UROD).¹⁴⁹ In the sporadic subtype (75% of cases), UROD activity is deficient only in the liver, whereas in the familial subtype (25% of cases), an autosomal dominant disorder at early-onset disorder affecting both sexes, the defect leads to a constitutive 50% UROD deficiency also in the erythrocytes.¹⁵⁰ Porphyria cutanea tarda is a complex disease in which both a multigenic predisposition and environmental risk factors are needed for clinical expressivity. The risk factors that contribute to inactivation or inhibition of this enzyme are mainly alcohol abuse, estrogens, hepatitis C, and to a lesser extent, HIV infections and inheritance of one or more *HFE* genotypes.^{151–153} Symptoms develop when residual, hepatic UROD decreases below a threshold of ~25%. Clinical features include photosensitive skin lesions, hepatic accumulation and urinary excretion of uroporphyrins, altered iron indices, and hepatic iron overload. Iron removal by phlebotomy is part of the current therapeutic strategy in PCT: It improves the clinical outcome and biochemical signs of the disease.¹⁵⁴

African Siderosis

African iron overload, formerly called Bantu siderosis,¹⁵⁵ is still an important pathology in rural society where up to 15% of adult males may be affected. It was originally described by Strachan in individuals from several parts of southern and central Africa in the 1920s.¹⁵⁶ Originally, iron overload was attributed to consumption of food, or more significantly to large quantities of traditional beer prepared in iron pots.¹⁵⁷ Later, a genetic modifier was postulated,¹⁵⁸ and a polymorphism of the ferroportin gene (p.Gln248His) restricted to Africans and African Americans has been considered a candidate modi-

fier,^{106,107} but no conclusive evidence has been provided so far. Regardless of a predisposing genetic trait, alcoholic beverages are a main factor leading to iron overload and liver disease in southern Africa's rural adult population. They may develop cirrhosis and HCC and liver iron concentration may reach the level found in *HFE*-HC and beyond.¹⁵⁹

Alloimmune (Neonatal) Hemochromatosis

Neonatal hemochromatosis (NH) is a severe neonatal disease characterized by stillbirth or neonatal liver failure in the antenatal or early neonatal period, usually within a period of hours to days postdelivery.¹⁶⁰ Intrauterine growth retardation, and associated placental edema and either oligohydramnios or polyhydramnios are common. The prevailing presentation is jaundice with coagulopathy, hypoglycemia, and hypoalbuminemia and high SF. Thus, diagnosis is made after exclusion of other causes of liver failure and may be confirmed by (1) salivary gland biopsy, which demonstrates excess iron; and (2) MRI, which typically shows iron deposition in liver, pancreas, and heart, but with sparing of the spleen.¹⁶¹ Various theories have been put forth to explain the etiology of NH, including fetal liver injury causing abnormalities of iron handling, or alternatively, abnormalities of iron handling by the maternofetal unit, with the possibility existing that they are not mutually exclusive.¹⁶⁰ There is a high rate of recurrence if a mother has a previous pregnancy complicated by NH; occasionally, it has been also documented in consanguineous families, which has been considered support that NH is a genetic disease. However, a candidate gene has not yet been identified. On the contrary, recently, an alloimmune mechanism for the disease has been postulated.¹⁶¹ Neonatal hemochromatosis may represent the phenotypic expression of gestational alloimmune foetal liver disease induced by the placental passage of specific reactive immunoglobulin G and involving the activation of fetal complement by the classical pathway leading to the formation of membrane attack complex as the effector of cell injury. Recently, Pan et al¹⁶² found that the percentage of hepatocytes containing antiterminal complement cascade neoantigens involved in membrane attack complex formation in NH was much greater than that in non-NH liver disease. In this vein, high-dose intravenous immunoglobulin therapy (IVIG) to the mother appears to significantly increase survival of newborns¹⁶³; high-dose IVIG, with or without exchange transfusions, to newborns achieved 75% good outcome compared with 17% in historical controls not treated with IVIG.¹⁶⁴ The prognosis of NH is extremely poor. Antioxidant therapy and chelation appear to be of limited value, and although liver transplantation has been identified as a viable therapeutic option, there may be reaccumulation of hepatic iron.¹⁶⁵

ABBREVIATIONS

CP	ceruloplasmin
DMTI	divalent metal transporter-1
FD	ferroportin disease
FPN	ferroportin
HAMP	hepcidin
HC	hemochromatosis
HCC	hepatocellular carcinoma
HJV	hemojuvelin
IVIG	intravenous immunoglobulin
JHC	juvenile hemochromatosis
KC	Kupffer cells
MRI	magnetic resonance imaging
NH	neonatal hemochromatosis
PCT	porphyria cutanea tarda
SF	serum ferritin
TFR2	transferrin receptor 2
TIBC	total iron binding capacity
TS	transferrin saturation
UROD	uroporphyrinogen decarboxylase

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